CLL IN FOCUS

Current Developments in the Management of Chronic Lymphocytic Leukemia

Addressing Cardiovascular Complications of BTK Inhibitors

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H&O What are the specific cardiovascular complications that are associated with Bruton tyrosine kinase (BTK) inhibitors?

JM Many cancer drugs have adverse effects on the heart and blood vessels. For example, trastuzumab, which is used in breast cancer, can cause heart failure; tyrosine kinase inhibitors that target BCR-ABL, which are used in chronic myeloid leukemia, have cardiovascular effects; immune checkpoint inhibitors, which are used in many forms of cancer, can lead to myocarditis; and vascular endothelial growth factor inhibitors can cause hypertension. These cardiac effects can be acute, occurring while the drug is being taken; they can also persist or appear after the drug has been withdrawn.

Regarding BTK inhibitors, we have seen multiple cardiovascular complications with ibrutinib (Imbruvica, Pharmacyclics/Janssen), including atrial fibrillation (AF), hypertension, ventricular tachycardia, atrioventricular dissociation, and heart failure. Ibrutinib is the first agent to be approved in this class, so we do not always know if these complications extend to the entire class of BTK inhibitors.

When we first saw evidence of AF among patients using ibrutinib, it was not clear that this complication was related to the agent. AF is fairly common among the general population, and even more so among people who have cancer or other illnesses.

Therefore, we conducted a meta-analysis with multiple collaborators across the country and around the world, including Dr Jennifer Brown of Dana-Farber Cancer Institute, to look at 1505 matched patients in 4 registration trials in which the only difference was whether the patient was receiving ibrutinib or placebo. This study, which appeared in *Haematologica* in 2017, found the incidence of AF to be 6.5% in the ibrutinib arm vs 1.6% in the comparator arm, a finding that pointed to a probable causal relationship between AF and ibrutinib, and possibly between AF and the entire BTK class. However, if a relationship exists between AF and acalabrutinib (Calquence, AstraZeneca) or between AF and zanubrutinib (Brukinsa, BeiGene), it appears to be much weaker than the relationship between AF and ibrutinib. In the ELEVATE-RR study, which Byrd and colleagues published in the *Journal of Clinical Oncology* in 2021, the rate of all-grade AF/atrial flutter was significantly lower with acalabrutinib than with ibrutinib: 9.4% vs 16.0%, respectively. The difference was even more striking among patients without a history of AF: 6.2% vs 14.9%, respectively. The ALPINE trial, which appeared in the *New England Journal of Medicine* in 2022 with Brown as the first author, also showed a lower incidence of AF with zanubrutinib (5.2%) than with ibrutinib (13.3%). We currently use the $CHADS_2$ score (heart failure, hypertension, age ≥75 years, diabetes mellitus, history of stroke or transient ischemic attack) to determine the risk of stroke in patients with AF, but this score has never been validated in patients with cancer. It is important to note that none of the above studies specifically looked for AF. Most people with AF had to have grade 3 or higher AF for it to be picked up in the studies. No surveillance testing (eg, cardiac event monitoring) was done. As a result, many cases of AF may not have been identified. What the field currently lacks is a detailed assessment of cardiac arrhythmias in patients on BTK inhibitors that measures the total burden of arrhythmia.

Hypertension, which seems to be a broad effect across the different BTK inhibitors, can increase the risk of stroke and cardiac complications. Ventricular tachycardia is also a major concern. In a study by Woyach and colleagues, which appeared in the *New England Journal of Medicine* in 2018, progression-free survival was better in the ibrutinib arms than in the control arm, but the rate of sudden death was significantly higher in the 2 ibrutinib arms than in the control arm. This is an important finding because ventricular tachycardia can lead to sudden cardiac death. Regarding the increase in heart failure, we do not know whether this is secondary to arrhythmias or caused by an effect on the heart itself. Again, it is unclear whether these complications are unique to ibrutinib or occur throughout the drug class.

H&O What are the mechanisms by which BTK inhibitors affect the heart?

JM Our laboratory is heavily invested in underlying basic and translational mechanisms in the field of cardio-oncology. One of the first questions in our laboratory is whether an effect is on target or off target. If a side effect is mediated by BTK, we would expect to see it across the entire drug class. What we have seen in both cell-based and mouse models is that many of the side effects of ibrutinib are off target and are mediated by C-terminal Src kinase (CSK) rather than by BTK. CSK is expressed in the heart, especially in the atria, which could be one reason why we see an increase in AF. The work to identify CSK as a target was led by Dr David Milan, who is currently at the Leducq Foundation for Cardiovascular Research. In my laboratory, we are now delineating the downstream targets of CSK and determining whether this signaling cascade is relevant to other forms of arrhythmia. If it is relevant, we may have uncovered a novel signaling strategy for AF that we hope will lead to potential therapeutics for AF.

H&O Does the addition of other agents to treatment affect the risk of cardiac complications?

JM Yes, we know that combining different drugs with cardiac effects can increase those effects. In a single-arm phase 2 study that Dr Jorge Castillo presented at the 2022 American Society of Hematology (ASH) annual meeting, the rate of ventricular arrhythmia or cardiac arrest with ibrutinib plus venetoclax (Venclexta, AbbVie/Genentech) in 45 patients with Waldenström macroglobulinemia was unacceptably high, at 9%. As a result, the study was halted early. It is important to note that venetoclax has not been associated with any obvious cardiovascular toxicity signals to date, so it is unclear why this combination was particularly arrhythmogenic.

> I would like to see more institutions set up cardio-oncology programs like the one we have here.

H&O What should doctors tell patients about the risk of cardiac complications with these drugs?

JM Oncologists need to discuss all the risks of BTK inhibitors with their patients, including cardiac complications. The difference in efficacy among these drugs is minimal, but the difference in terms of the risk of arrhythmias does seem to be clinically significant. Patients should be aware not only of the risk of arrhythmias but also of how arrhythmias may present clinically, so that they know what to be on the alert for.

H&O Should the choice of agent differ depending on the patient's risk factors for cardiac complications?

JM Absolutely. Age is the number one risk for most cardiovascular diseases. Similarly, the prevalence of AF increases with age, especially age older than 65 years. The ATRIA study by Go and colleagues, for example, which looked at 1.9 million people, found an overall prevalence of AF of 1%. The prevalence of AF ranged from 0.1% among adults younger than 55 years to 9% in those 80 years or older. Seventy percent of those with AF were at least 65 years old, and 45% were at least 75 years old. In addition, people who have existing heart disease or who have already experienced AF are at increased risk for experiencing AF again, so I would choose acalabrutinib or zanubrutinib over ibrutinib for these patients. Even for patients who are not at especially high risk, I would choose a drug that causes less arrhythmia over one that causes more arrhythmia, all other things being equal.

H&O What sort of monitoring should be done for cardiac complications?

JM The jury is still out regarding official recommendations, but all patients should undergo electrocardiography

before beginning treatment with a BTK inhibitor or any other systemic anticancer agent. Some physicians may also order an echocardiogram. After that, I recommend the use of a cardiac event monitor in patients who have an underlying heart disease, such as AF or cardiomyopathy. Another fact to bear in mind is that BTK inhibitors increase the risk of bleeding, which is of special concern because anticoagulation is the standard treatment for AF.

H&O How often is cardiac event monitoring used in patients with cancer?

JM Cardiac event monitoring is not used in patients with cancer very often. There is a pressing need to carry out studies in which cardiac event monitoring is used to assess the arrhythmia burden associated with BTK inhibitors.

H&O How do you proceed if a cardiac complication develops in a patient taking a BTK inhibitor?

JM Of course, I should first mention that AF can be very manageable. Drugs such as beta blockers decease the heart rate, and anticoagulation can decrease the risk of stroke when used in the right individuals. Of course, at this point the patient should be referred to cardio-oncology. Then, the question from oncology is whether to hold the BTK inhibitor or even switch to a different BTK inhibitor. If we started with ibrutinib, it would certainly be logical to switch to another BTK inhibitor, but it is still worth switching from acalabrutinib to zanubrutinib and vice versa. We should not halt the use of BTK inhibitors and handcuff our oncologist colleagues because of AF. Instead, the oncologist should refer any such patient to a cardiologist who is familiar with BTK inhibitors—a cardio-oncologist—and who knows how to treat the AF without stopping the medication. This is an area in which collaboration across different disciplines makes a large difference in patient care, and I would like to see more institutions set up cardio-oncology programs like the one we have here at the University of California, San Francisco. I think it is fair to say that BTK inhibitors have been game changers in the treatment of patients with chronic lymphocytic leukemia, and we want as many patients to benefit from them as possible.

Additional BTK inhibitors are already being developed; my only concern is that the studies submitted to the US Food and Drug Administration focus far more on efficacy than on cardiac effects.

Disclosure

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Suggested Readings

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